

UNITED STATES DISTRICT COURT  
FOR THE  
DISTRICT OF VERMONT

ALZA CORPORATION and	:	
JANSSEN PHARMACEUTICA, INC.	:	
	:	
Plaintiffs,	:	
	:	
v.	:	Case No. 2:02-cv-20
	:	<b>Consolidated with</b>
MYLAN LABORATORIES, INC.,	:	Case No. 2:02-cv-213
MYLAN TECHNOLOGIES, INC., and	:	
MYLAN PHARMACEUTICALS, INC.,	:	
	:	
Defendants.	:	

**FINDINGS OF FACT AND CONCLUSIONS OF LAW**

Plaintiffs Alza Corporation ("Alza") and Janssen Pharmaceutica, Inc. ("Janssen") brought suit for infringement of United States Patent No. 4,588,580 and its two Reexamination Certificates ("the '580 patent") against Defendants Mylan Laboratories, Inc., Mylan Technologies, Inc., and Mylan Pharmaceuticals, Inc. ("Mylan"). Mylan counterclaimed, asserting that its product does not infringe the '580 patent, and that the '580 patent is invalid. The Court conducted a nine-day bench trial between August 25 and September 5, 2003. The following constitutes the Court's findings of fact and conclusions of law as required by Rule 52(a) of the Federal Rules of Civil Procedure.

## **FINDINGS OF FACT**

### **I. Introduction**

The '580 patent discloses systems for the transdermal administration of fentanyl, a powerful narcotic, for an extended period of time at analgetically effective rates. The '580 patent, issued on May 13, 1986, was developed by a team of Alza scientists headed by Robert Gale. Janssen sells an embodiment of the '580 patent as the Duragesic® patch. The Duragesic® patch has transformed the treatment of chronic pain. Patients suffering from a variety of painful and debilitating conditions, including terminal cancer, can obtain relief without hospitalization for up to three days from the application of a single patch. Duragesic® has been a huge commercial success for Alza and Janssen and their parent company Johnson & Johnson.

Mylan has developed a generic transdermal fentanyl patch that is bioequivalent to Duragesic®. It has filed an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA"), seeking approval to market its patch before Alza's '580 patent expires. See 21 U.S.C.A. § 355(j) (West 1999).

### **II. The Development of Transdermal Administration of Drugs**

Although transdermal medication is not a new science, controlled-rate transdermal administration of drugs for a sustained period of time is a relatively recent development. Because the skin is a particularly effective barrier to the transmission of foreign substances into the body, relatively few drugs have been found to be suitable for transdermal administration. Thousands of compounds have been evaluated for possible transdermal delivery, but today only eleven transdermally administered drugs are on the market. In 1984, when the '580 patent application was filed, only three drugs were available transdermally: scopolamine, nitroglycerin and clonidine.

Alza was a pioneer in the development of transdermal drug delivery, and was the first company to develop a transdermal system for seven of the eleven drugs currently on the market. Experts in the field agree that transdermal delivery poses "as stringent a set of expectations as exists for any pharmaceutical system, and achieving all of [the] requisite features for one system all at the same time is truly a technological accomplishment." G.L. Flynn & N.D. Weiner, Topical and Transdermal Delivery--Provinces of Realism, in Dermal and Transdermal Delivery 33, 58 (R. Gurny ed., 1993) (Pls.' Ex. 481,

hereafter "PX \_\_\_\_"). To be suitable for transdermal delivery, a drug must be potent and skin permeable. A transdermal patch must be able to deliver the drug at an adequate and reasonably constant rate for a sustained period of time, should not irritate the skin or provoke an allergic reaction, and "ideally, should efficiently deliver most of the drug [it] contain[s]." Id. at 57.

The fundamental idea behind transdermal delivery systems was to use a saturated solution, with excess undissolved drug available to replace the drug that left the solution when it penetrated the skin. In 1984, conventional wisdom indicated that a promising candidate for transdermal delivery would have high solubility, since more drug in solution meant a greater ability to push the drug through the skin, and a high permeability coefficient. The permeability coefficient of a substance is calculated by measuring its flux, meaning its ability to move through the skin per unit area, and its concentration. Prototypical transdermal patches would contain huge excesses of drug, only a fraction of which would be delivered to the patient, in order to assure a constant rate of transmission.

### **III. Alza's Development of a Fentanyl Transdermal System**

In 1981 Alza responded to a plea from a White House-created committee of scientists and physicians to develop more potent analgesics in alternative delivery systems for critically ill and dying patients who were suffering from intractable pain. Alza wrote to the head of the Drug Abuse Unit of the FDA, expressing its interest in developing a transdermal dosage form for delivery of a narcotic analgesic for relief of chronic pain, and inquiring about the extent of clinical testing that would be required to bring such a product to market. Alza began work on a project to develop a fentanyl transdermal patch in late 1982. A feasibility development team, headed by Dr. Su Il Yum and Dr. Eun Soo Lee, performed the initial research on the patch, beginning in 1983. Late in 1983 the feasibility team recommended further development of the product, and transferred the project to a product development team led by Robert Gale and Victor Goetz.

In early 1983 Alza representatives met with agents from the United States Drug Enforcement Administration to discuss the handling of fentanyl. Among other issues, the agency expressed concern that the dosage be kept to an absolute minimum, because of the potential for diversion and abuse of such a potent narcotic. Before the advent of the transdermal patch, fentanyl

had only been administered in hospital settings, where the opportunities for abuse were largely limited to hospital personnel with access to the drug. Large excesses of fentanyl remaining in discarded patches would substantially increase the risk of abuse. Minimizing residual drug accordingly became the focus of Alza's fentanyl patch project, along with maximizing skin flux.

Alza discovered that the base form of fentanyl satisfied both criteria. Dr. Lee had reviewed the results of research conducted by Alza scientists in the 1970s who had evaluated numerous compounds as candidates for transdermal systems, including fentanyl. From his review of their research he reported that maximum skin fluxes could be obtained at pHs of 7 to 8. Within that range of pH, however, dramatically different amounts of fentanyl were required to achieve those fluxes, with far lower concentrations at the higher pHs. Dr. Lee concluded that "[i]n general, much higher flux is observed with base Fentanyl than its citrate salt. It would be recommended to pursue studying with base drug." (PX 10, Attach. 3.) His recommendation reflected two realizations: one, that saturated solutions of fentanyl could be obtained using far less drug at higher pHs; and two, that the permeability coefficient of

fentanyl increases with an increase in pH. A high permeability coefficient permits the use of lesser amounts of drug to achieve adequate flux through the skin.

This information represented a departure from the traditional expectation that drugs of high solubility were better suited for transdermal systems because of their enhanced skin permeability. See A.S. Michaels et al., *Drug Permeation Through Human Skin: Theory and in Vitro Experimental Measurement*, 21 AIChE J. 985, 986 (1975) (PX 6).

The decision to use base fentanyl drove the other design considerations. The feasibility team developed three patch prototypes, all using fentanyl base. One form was a monolith, in which a simple fentanyl/adhesive mixture was used. The second system was a multilaminate, in which a priming dose of fentanyl was dissolved in the adhesive, with a separate drug reservoir and a rate-controlling membrane to control the flow of drug. The third design was a form-fill seal, in which fentanyl was dissolved in an ethanol/aqueous solution. This design also featured a rate-controlling membrane. Only the multilaminate and the form-fill seal systems were forwarded to product development. Alza concluded that systems with a rate-

controlling membrane were preferable, given the fear of potential overdosing.

Robert Gale and his product development team took over responsibility for the project in December 1983. They continued to concentrate on minimizing the amount of drug in the system. This goal led the team to focus on an ethanol form-fill seal design, because they could further reduce the size of the system and minimize drug content. See Goetz Milestone I Report at 1 ("need to keep both residual drug and lag time to a minimum forced selection of an ethanol form-fill-seal design for [fentanyl] product development") (PX 146). Although adding ethanol to the solution increased its solubility, ethanol worked as a skin permeation enhancer, and even with an increase in solubility the system's drug content was reduced. The addition of ethanol also reduced the lag time for the drug to reach therapeutic levels in the body, another important design consideration.

Eventually the inventors were able to produce a fentanyl patch that delivered 72% of its drug load to the patient, an excess of 1.38 times the amount of delivered drug. At a meeting with parties from the FDA, the DEA and The National Institute on Drug Abuse in 1990, Alza demonstrated that the amount of



fentanyl that could be extracted from its used patches would be a noneuphoric dose for addicted users. A medical reviewer for the FDA concluded that Alza had successfully addressed potential abuse issues by minimizing the amount of drug in the patch.

On August 7, 1990, the ethanol form-fill-seal design was approved for the management of chronic pain in patients who required round the clock dosing that couldn't be managed by less potent analgesics. Alza entered into a licensing agreement with Janssen to market the patch as Duragesic®.

Alza's scientists also had to determine a safe and effective dose for transdermal fentanyl. When Alza undertook the fentanyl project in 1983, fentanyl was used principally as an anesthetic, not an analgesic. As an analgesic most published reports described the use of bolus doses<sup>1</sup> administered intramuscularly, and therefore were not necessarily an indicator of a safe and effective continuous transdermal dose. Intravenous infusion data was considered the most useful information for predicting transdermal dosage, but at the time the available intravenous data included patient self-administration of bolus doses. See e.g., C.J. Hull & A.

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<sup>1</sup> Large single doses injected over a short period of time.

Sibbald, Control of Postoperative Pain by Interactive Demand Analgesia, 53 Brit. J. Anaesth. 385 (1981) (Defs.' Ex. 1193, hereafter DX \_\_\_\_); B. Kay, Postoperative Pain Relief, 36 Anaesthesia 949 (1981) (DX 1168); W.D. White, et al., Postoperative Analgesia: a Comparison of Intravenous On-Demand Fentanyl with Epidural Bupivacaine, 2 Brit. Med. J. 166 (1979) (DX 1176). The references reported intravenous dose rates that ranged between 30 and 150 µg/hr. At that time the longest use of fentanyl reported in the literature was a post-operative period of seventeen hours. See White, et al. at 167. The Alza inventors were concerned about the effect of longer term use of fentanyl, whether fentanyl built up to dangerous levels in the body over time, or whether patients developed a tolerance to the drug with chronic use. The scientists at Alza also needed to ascertain whether fentanyl, delivered transdermally, would have a reasonably prompt onset of action.

To attempt to answer these questions, Alza commissioned continuous IV infusion therapy studies in an attempt to determine the dose ranges for a transdermal system. After Alza reviewed reports from the continuous IV studies, it conducted pharmacokinetic and safety and efficacy studies in both acute

and chronic patient populations in dosages ranging from 25 to 600 µg/hr.

In 1991, ten years after Alza proposed developing a transdermal fentanyl patch, Duragesic® was made available for sale in the United States. Duragesic® is the only commercial embodiment of the '580 patent sold in the United States, and it has enjoyed tremendous commercial success. For the year 2003, net trade sales were projected to exceed \$1 billion, based upon gross sales of greater than \$1.2 billion. These figures make Duragesic® one of the best selling pharmaceutical products in the world.

#### **IV. The '580 Patent**

The '580 patent application was filed in the summer of 1984, and issued on May 13, 1986. '580 patent (PX 1). At the time, Alza had developed three embodiments of its patch, the monolith, the multilaminate, and the form-fill seal. The patent describes its "field of invention" as relating to "the administration of fentanyl for analgetic purposes and more particularly to a method and device for administering fentanyl to a subject through intact skin over an extended period of time at a substantially constant rate." Id. at 1:6-10. In the patent's background section, it describes fentanyl as an

extremely potent and effective anesthetic and analgesic. Id. at 1:13-17. It refers to the patent that discloses the drug fentanyl and the 1984 Physician's Desk Reference for the FDA-approved use of the drug in the United States under the name SUBLIMAZE®. Id. at 1:17-22. It describes the usual use of fentanyl: "[i]n use, fentanyl is normally administered as the citrate either as a bolus injection or infusion or a continuous infusion for the purposes of producing anesthesia or analgesia." Id. at 1:22-25.

The patent addresses the characteristics of fentanyl that pose a challenge to the design of a transdermal delivery system: its narrow therapeutic index, its cost, and the high potential for abuse, id. at 1:47-55, and it states as one of the objects of the invention "to provide transdermal therapeutic systems for the administration of fentanyl or its derivatives in which the amount of residual drug is minimized." Id. at 2:23-26.

The inventors proceeded to describe the key to their invention:

[w]e have found that there is a relatively wide range of permeability of normal human skin to fentanyl and this permeability not only varies from individual to individual and site to site but is also highly dependent on the chemical form of the drug. We have discovered that fentanyl citrate, the form in which fentanyl is presently

administered, has such a low skin permeability that it is not at all suitable for transdermal delivery even with the use of permeation enhancers. Instead we have found that, in order to obtain the delivery rates noted above, the drug should be incorporated in the transdermal therapeutic system in the form of the base.

Id. at 3:6-17.

In the description of their invention, the inventors thus excluded the administration of fentanyl citrate, the form in which fentanyl was at that time administered. At the time, fentanyl was administered as SUBLIMAZE®, a solution with a pH of 4.0 to 7.5. Physicians' Desk Reference 1027 (38th ed. 1984) (PX 541). The pKa, the pH at which a solution contains fifty percent acid and fifty percent base, has been experimentally determined for fentanyl at pH 8.3 or higher. At a pH of 7.0, a fentanyl solution is 95% or more fentanyl citrate, the ionized or acidic form of fentanyl. The authors of the '580 patent were stating that, for purposes of their invention, they were excluding solutions of fentanyl that were predominantly citrate, those with a pH of 7.5 or less. As subsequent research has borne out, although fentanyl has a measurable flux at lower pHs, the base form of fentanyl is almost entirely responsible for fentanyl's permeation through skin. Samir D. Roy & Gordon L. Flynn, Transdermal Delivery of Narcotic Analgesics, 7

Pharmaceutical Research 842, 845-846 (1990) (PX 28). As Mylan's expert Dr. Flynn concluded: "[n]ot suprisingly, the free-base form is the permeable form of [fentanyl]." Id. at 847.

The patent describes seven examples of specific embodiments of the invention, including examples of the form-fill seal, the multilaminate, and the monolith, all of which use the base form of the drug. The original patent contained 58 claims, some of them directed to the process of inducing and maintaining analgesia through the transdermal administration of fentanyl, and some of them directed to a medical device for that administration.

The '580 patent has undergone two reexaminations, once in 1987 and again in 1998. Alza requested the first reexamination in light of the 1975 Michaels article, Drug Permeation Through Human Skin, which had not been specifically identified to the Patent Office as a prior art reference. Michaels et al. had attempted to construct a model for predicting the rate of absorption of drugs through skin from a knowledge of certain physicochemical properties of the drugs. The researchers tested ten drugs, including fentanyl, and determined their flux rate through cadaver skin. They concluded that drugs of high water and oil solubility could be expected to be quite skin permeable.

Fentanyl, with low water solubility, would thus not be expected to be particularly skin permeable, according to the Michaels model. The article included a table summarizing the results of the flux studies, that showed flux ranges for fentanyl and the other drugs studied.

Eventually the Examiner confirmed the patent claims as amended and allowed 52 new claims. (PX 5, v. 2, tab 20.) The Examiner reasoned:

The use of transdermal devices as recited in the instant claims is not deemed to be obvious . . . [i]t cannot be clearly ascertained from Michaels et al . . . that fentanyl and its derivatives would be suitable for transdermal administration at an analgetically effective level. Michaels et al . . . teaches that "drugs of high water and oil solubility can be expected to be quite skin permeable." Yet . . . fentanyl has a low water solubility. Thus, the reference can only be viewed as supporting the known unpredictability of the choice of drug which may be suitable for transdermal administration.

Id. at 2. The first reexamination certificate issued on January 3, 1989. (PX 2.)

In late 1997 or early 1998 Alza attorney Steve Stone learned of a patent for a "polymeric diffusion matrix" issued to Alec D. Keith and Wallace Snipes on September 11, 1984. The Keith patent (PX 9) disclosed a polymeric diffusion matrix suitable for transdermal drug delivery. In the description of

the invention Keith and Snipes state that "any drug which is capable of being transdermally or topically administered to a patient may be dispersed in the diffusion matrix." Keith patent at 3:41-44.

The Keith patent is directed principally at making a nitroglycerin patch, and teaches that for a 24-hour patch an approximate ten-fold excess of the drug should be included in the matrix. Id. at 4:35-37. N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide, the chemical name for fentanyl, is mentioned as one of dozens of drugs that are considered suitable for inclusion in the diffusion matrix. Id. at 3:54-55. The patent actually states that "[i]t is contemplated that any drug which may be transdermally applied is suitable for use as the drug to be applied via the diffusion matrix in the present device." Id. at 4:16-19. The patent's example VI also refers to fentanyl: "[b]y substituting an appropriate amount of [fentanyl] in place of the [nitroglycerin mixture], otherwise following the procedure of Example I, a diffusion matrix is obtained." Id. at 11:57-60. There is no other discussion or explanation of the use of fentanyl in a transdermal delivery system. None of the Keith patent claims cover fentanyl.



Stone asked Gale to review the Keith patent. Gale found that the Keith patent disclosed two methods for producing the diffusion matrix. Both methods involved adding suitable amounts of sodium citrate and citric acid to the matrix in order to adjust the pH of the mixture to be neutral or slightly acidic, in the range of pH 6.5 to 7.0. (Gale Decl. ¶ 6 (PX 10); Keith patent at 5:28-6:6.) Gale also noted that the Keith patent disclosed substituting an appropriate amount of fentanyl in place of a mixture of lactose and nitroglycerin, but did not disclose what that amount was, nor how it was to be determined. (Gale Decl. ¶ 7.) Gale concluded that the patent required that the drug in solution be maintained at that pH range, regardless of the amount of drug to be added to the solution. Other reviewers of the Keith patent agreed: Keith describes a matrix that contains a drug in solution at a pH of 6.5 to 7.0. (Langer Test. 8/29/03, vol. I at 124 (hereafter \_\_\_\_\_ (date), (vol. no.) at \_\_\_\_); Flynn 9/3/03, I at 79; Hadgraft 9/5/03, I at 37.) A matrix containing fentanyl at pH 6.5 to 7.0 would be almost entirely fentanyl citrate--at least 95% fentanyl citrate and 5% or less fentanyl base.

Gale signed a Declaration for the Patent Office, distinguishing the Keith patent from his invention, and stating

that "to the extent that the Keith patent could be considered to disclose making a transdermal fentanyl delivery system by including fentanyl in the diffusion matrices of the Keith patent, such a system would be unsuitable for administering fentanyl at analgetically effective rates," because the fentanyl present in the Keith matrix would exist virtually completely in the form of fentanyl citrate. (Gale Decl. ¶ 9.) Gale also stated that

the Keith patent suggests the production of a diffusion matrix containing fentanyl citrate, which we specifically stated in the '580 patent was unsuitable for transdermal delivery, even with permeation enhancers. It is clear to me from reading the Keith patent that Keith et al. had no appreciation of . . . the difference between the use of fentanyl citrate and forms of fentanyl suitable for transdermal administration.

Id. ¶ 11. Gale concluded: "I believe that the disclosure of the Keith patent would not suggest to or enable one of ordinary skill in this art to make and use a device or process that would transdermally administer a 'skin permeable form' of fentanyl (or derivatives thereof) to a human at an analgetically effective rate for a period of time sufficient to induce and maintain analgesia." Id. The quoted reference to a "skin permeable form" of fentanyl is an explicit reference to the language of

the '580 patent, in which each claim specifies "a skin permeable form" of fentanyl.

Gale's declaration referred to the Alza research from the 1970's and Dr. Lee's review of that research in 1983, and attached copies of the lab notebook entries and Dr. Lee's memo. Gale characterized the research as supporting "the conclusion that the skin permeability of fentanyl citrate was too low to permit analgetically effective transdermal fentanyl administration rates to be obtained from reasonably sized transdermal systems." Id. ¶ 12. It quoted and concurred with Dr. Lee's conclusion that "[i]n general, much higher flux is observed with base Fentanyl than its citrate salt. It would be recommended to pursue studying with base drug." Id. ¶ 13.

The Patent Examiner re-confirmed the claims of the '580 patent, observing that both the '580 patent and a prior art Japanese patent disclose that fentanyl citrate has a very low level of transdermal permeability, and Gale's interpretation of the Keith patent indicates that it produces fentanyl in the citrate salt form. (PX 8, tab 8.) The Examiner concluded that

the Keith et al reference fails to teach one having an ordinary skill in the art to make and use a device which would transdermally administer a skin-permeable form of fentanyl (or its derivatives) to a human subject at an anagetically

[sic] effective rate and for a sufficient period of time to induce and maintain analgesia as taught by the patent in Re-examination.

Id. The second reexamination certificate issued on February 16, 1999. (PX 8, tab 9.)

At the request of the FDA, Alza recently undertook pediatric studies, three to four years of clinical trials of Duragesic®'s suitability for the treatment of chronic pain in severely ill children. As a result of the studies, the FDA has extended Duragesic®'s period of market exclusivity for an additional six months from the expiration date of the '580 patent. See 21 U.S.C.A. § 355a(b) (West Supp. 2003).

#### **V. The Mylan Fentanyl Patch**

Mylan is one of the nation's largest manufacturers of generic pharmaceutical products. A company seeking to market a generic drug may obtain FDA approval by demonstrating that its product is bioequivalent to an approved drug that has already been shown to be safe and effective. See 21 U.S.C.A. § 355(j)(2); see also Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322, 1325-26 (Fed. Cir. 2003) (summarizing shortened FDA approval process for generic drugs under Hatch-Waxman Act's amendments to the Food, Drug and Cosmetic Act).

Mylan set out to develop a fentanyl transdermal system that is bioequivalent to Duragesic®. It tested both multilaminate and monolith formulations. Eventually it settled on a monolith drug-in-adhesive design, using fentanyl alkaloid powder, which is fentanyl base. Bioequivalence and wear studies of Mylan's 25 µg/hr fentanyl patch showed that it delivered fentanyl to patients in the same way and at the same rate as Duragesic®. (PX 35 at 13.) Mylan's generic patch also minimized the amount of excess drug in the patch.

Under the Hatch-Waxman Act's amendments to the Food, Drug and Cosmetic Act, a company seeking to market a generic version of a drug previously approved by the FDA may file an ANDA, certifying that its generic drug is bioequivalent to the branded drug, and certifying that manufacturing, marketing and selling the drug will not infringe on any patent rights. See 21 U.S.C.A. § 355(j). The applicant who makes such a certification must notify each owner of a patent that is the subject of the certification. Id. § (j)(2)(B).

Mylan submitted an ANDA to the FDA on October 12, 2001 for approval to market its generic fentanyl patch. (PX 536.) In connection with the ANDA, Mylan provided a "Paragraph IV" certification, stating that its fentanyl transdermal patch will

not infringe the '580 patent, and that the '580 patent is invalid. See id. (j)(2)(A)(vii)(IV). It gave notice to Alza of its Paragraph IV certification, as required by the statute. See id. § (j)(2)(B). This suit for infringement followed.

#### **VI. Construction of a Keith Diffusion Matrix for Purposes of Invalidating the '580 Patent**

Mylan takes the position that its product does not infringe the '580 patent, but it also argues that the Keith patent is invalidating prior art, notwithstanding the contrary determination of the Patent Examiner. To prove its point, Mylan decided to attempt to create a fentanyl diffusion matrix according to the teachings of the Keith patent, and to ascertain whether a Keith patch would deliver an analgetically effective amount of fentanyl over an extended period of time at a substantially constant rate.

Mylan asked Dr. Gordon L. Flynn, a leading expert in the field of transdermal drug delivery, to make a fentanyl transdermal matrix in accordance with the teachings of the Keith patent. Dr. Flynn attempted to make the matrix from the perspective of an individual of ordinary skill in the transdermal art as of the 1983-1984 time period. He examined the Keith patent's Example I, which gives the recipe for the

diffusion matrix. He examined the patent's Example VI, which directs one to substitute an appropriate amount of fentanyl for lactose triturate and otherwise to follow the procedure set forth in Example I, in order to make a diffusion matrix.

He then set about determining what an appropriate amount of fentanyl would be. In column four of the Keith patent he found the statement that

[t]he amount of the drug dispersed in the diffusion matrix can be varied in accordance with the desired dosage and the length of time the matrix is to remain on the skin. However, the amount of the drug included in the matrix should generally be in excess of the amount which is to be delivered to the patient. If the diffusion matrix is to be used for 24 hours, an approximate 10 fold excess of the drug should be included. . . . Quite obviously, the optimum amount that should be included in the diffusion matrix will vary according to factors such as the period of release of the drug.

Keith patent at 4:30-46. The Keith patent did not discuss drug amounts for matrices that were to be used for longer than 24 hours. Dr. Flynn concluded that the Keith patent taught that an appropriate amount of fentanyl to add to the matrix "would be an amount of fentanyl that would produce analgesia over a prolonged period of time, then adjusted by tenfold higher in order to have the excess that he teaches in the system." (Flynn 9/2/03, II at 103.)

Dr. Flynn recognized that the patent did not give a specific dosage amount. To determine the desired dosage of fentanyl he consulted the available literature. At the time there were no studies regarding the transdermal administration of fentanyl to humans for analgesia, although intramuscular injection and intravenous infusion studies existed. From his literature review Dr. Flynn identified a range of therapeutic doses from 25 to 150  $\mu\text{g/hr}$ . From that range he selected a dose of 100  $\mu\text{g}$  "as a first estimate." (Flynn Notebook (PX 14) at 3.) He acknowledged that those of skill in the art at the time might have chosen rates that were lower than 25 and higher than 150  $\mu\text{g/hr}$ , and that nothing in the Keith patent required or even suggested the 100  $\mu\text{g/hr}$  dose.

Dr. Flynn selected three days as an appropriate period of time for the patch to be worn, based on the types of patches that were then on the market or in development. He acknowledged, however, that the longest continuous dosing of fentanyl reported in the literature was seventeen hours, and that the literature was silent on the safety or efficacy of continuous administration of fentanyl for three days.

Dr. Flynn then proceeded to create a matrix based on the Keith recipe. He mixed glycerol and water with sodium citrate



and adjusted the pH to 7.0 by adding citric acid. He heated the mixture and added polyvinyl alcohol and polyvinylpyrrolidone. He took 80 ml of this solution and added 2.525 grams of fentanyl base,<sup>2</sup> stirred the mixture until homogeneous and then poured it into petri dishes and allowed it to cool. Although the pH of the final solution wasn't tested, Dr. Flynn believed that the pH wouldn't vary much from the 7.0 or less to which it was initially adjusted. At pH 7.0 the fentanyl in solution was 95% ionized, or fentanyl citrate.

The Keith patent specified that a preferred aspect of the diffusion matrix be formed into squares having a surface area of about 6.5 cm<sup>2</sup>, and Dr. Flynn cut his test patches to this size. He then performed *in vitro* flux tests of the patches. Instead of his selected therapeutic rate of 100 µg/hr., the 6.5 cm<sup>2</sup> patch achieved a rate of 6.5 µg/hr. From this delivery rate Dr. Flynn deduced that a 25 cm<sup>2</sup> patch would deliver 25 µg/hr., the

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<sup>2</sup> Dr. Flynn calculated the amount of fentanyl to add to the solution by dividing .072 grams (the amount of fentanyl the three-day Keith patch should contain in order to deliver at the rate of 100 µg/hr.) by the area of the desired patch (6.5 cm<sup>2</sup> x .35 mm thick) and then multiplying by the volume of the solution. (Flynn Notebook at 3; Flynn 9/2/03, II at 114-116; 9/3/03, I at 88-90.)

low end of the range of dosages he had gleaned from the literature.

Mylan then employed researchers at the University of Michigan to use Dr. Flynn's notes to create batches of Keith matrices. The amount of fentanyl in the matrices doubled, from 72 mg in Dr. Flynn's formula to 145 mg in a 9 cm<sup>2</sup> patch. Keith's "appropriate amount" of drug to add to the diffusion matrix is based on the intended rate of drug delivery and duration of wear, not on the matrix's size or volume, and Mylan offered no reason why its scientists added more drug with an increase in patch size. Moreover, Mylan's researchers failed to follow every step of Dr. Flynn's lab notes, neglecting to revise his calculation of the "appropriate amount" of fentanyl to add when they altered the patch size. See Flynn Notebook at 3 (indicating that amount of fentanyl is to be divided by patch size).

Mylan conducted in vitro flux studies with the Keith matrices, and concluded that a 7 to 15 cm<sup>2</sup> patch should deliver in 72 hours an amount of fentanyl across skin that is comparable to Duragesic®. Mylan then decided to conduct clinical trials of the Keith matrix, that contained at this point not merely a ten-fold excess of drug, but something like a twenty-fold excess of

drug if a 100 µg/hr delivery rate were chosen, and an eighty-fold excess of drug if a 25 µg/hr rate were chosen.

As one Mylan scientist noted, the Keith matrix flux data showed a variable delivery of the drug, and could result in a delivery of up to four times the average for Duragesic® over a two to three-day period. (Rackley Review (PX 539) ¶ 5.) In connection with clinical trials for Mylan's own generic patch, the FDA had ordered Mylan to test only the lowest approved dose (25 µg/hr) of fentanyl transdermal patches on healthy human subjects because of the risk of respiratory depression on patients who have not previously been on opioid therapy. To reduce the risk to the subjects in this clinical trial of the Keith patch, Mylan nearly tripled the amount of anti-opiate they received.

The clinical trial protocol for the Keith matrix stated that the subjects were receiving a single 25 µg/hr dose of either Mylan's Keith matrix or Duragesic®. According to the teachings of Keith as interpreted by Dr. Flynn, a matrix designed to deliver 25 µg/hr. of fentanyl for three days should contain 18 mg of the drug (25 µg/hr x 72 hours x 10). The mean fentanyl content of the matrix patch used in the clinical trial

was 145.5 mg of fentanyl per patch (PX 15 at 1), eight times the amount taught by Keith as interpreted by Dr. Flynn.

The study concluded that, when worn for three days, the matrix delivered 40% more fentanyl systemically than Duragesic®. (PX 22 at 4.) However, the Keith matrix did not induce analgesia until at least fourteen hours after the patch was placed on the body. And once the Keith matrix started delivering fentanyl, the subjects' blood levels continued to climb throughout the period of application. Mylan's Keith patch therefore did not demonstrate bioequivalence with Duragesic®, but the Mylan scientists were only trying to show that a Keith patch, if loaded with enough fentanyl, could deliver the drug at an analgetically effective rate for an extended period of time.

### **CONCLUSIONS OF LAW**

#### **I. Infringement of the '580 Patent**

Alza asserts that Mylan is liable for infringement under 35 U.S.C.A. § 271(e)(2) (West 2001). Section 271(e)(2) of Title 35 defines as an act of infringement the submission of an ANDA containing a Paragraph IV certification "that is in error as to whether commercial manufacture, use, or sale of the new drug (none of which, of course, has actually occurred) violates the

relevant patent." Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 678 (1990).

At trial Alza reduced the number of claims it was asserting against Mylan to four: claims 59.11, 59.15, 61.31 and 27.25.<sup>3</sup>

Claims 59.11 and 59.15 are process claims. With the dependencies included Claim 59.11 reads as follows:

A process for inducing and maintaining analgesia in a human being by the transdermal administration of [fentanyl base] which comprises: transdermally administering to said human being through an area of intact skin, a skin permeable form of said [fentanyl base] at an analgetically effective rate and continuing the administration of said [fentanyl base] to said human being at said rate for an extended period of time at least sufficient to induce analgesia; wherein said extended period of time is in the range of [at least about 3 days] to 7 days.

Claim 59.15 is identical to Claim 59.11, but adds a further limitation "wherein the steady state administration rate of said [fentanyl base] is maintained within the range of about 25 to 150 µg/hr for a substantial portion of said [at least about 3 days]." Claims 61.31 and 27.25 are device claims. Claim 61.31 reads as follows:

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<sup>3</sup> The claim numbers describe dependent claims; for example, Claim 59.11 describes Claim 59 as it depends from Claim 11.

A medical device for inducing and maintaining analgesia in a human being by the continuous transdermal administration to a human being of [fentanyl base] at an analgetically effective administration rate and [for at least about 3 days] comprising, in combination:

(a) a reservoir for said [fentanyl base] having a skin proximal, material releasing surface area in the range of about 5-100 cm<sup>2</sup>, said reservoir containing between 0.1 and 50% by weight of a skin permeable form of said [fentanyl base] in amounts and at a concentration adequate to permit delivery of said [fentanyl base] through the intact [skin] of said human being at a flux within the range of from 0.5 to 10 µg/cm<sup>2</sup>/hr for at least about 24 hours; and

(b) means for maintaining said reservoir in material transmitting relationship to said skin.

Claim 27.25 reads as follows:

A medical device for the transdermal administration to a human being of [fentanyl base] at an analgetically effective rate for an extended period of time of at least about 24 hours and sufficient to induce and maintain analgesia which comprises:

(a) reservoir means containing a skin permeable form of [fentanyl base] in an amount sufficient to deliver said [fentanyl base] at said analgetically effective rate for said extended period of time; and,

(b) means for maintaining said reservoir means in material transmitting relationship to an area of intact skin on said human being, wherein said area is in the range of about 5-100 cm<sup>2</sup> and the device delivers said [fentanyl base] through the skin of said human being at a flux within the range of about 0.5-10 µg/cm<sup>2</sup>/hr.

#### **A. Claim Construction**

This Court issued an Opinion and Order on August 14, 2003 in which it construed seven terms or phrases that were disputed by the parties: 1) "inducing and maintaining analgesia;" 2) "analgetically effective rate;" 3) "area of intact skin;" 4) "steady state administration rate;" 5) "a substantial portion of said extended period of time;" 6) "reservoir;" and 7) "means for maintaining." Alza Corp. v. Mylan Labs., Inc., No. 02-cv-20 (D. Vt. Aug. 14, 2003) (order granting in part, denying in part motion for interpretation of patent claims). The Court did not address the definition of "skin permeable form" in its opinion, because the parties had agreed on a definition: "fentanyl that is in a form that can pass through the skin."

At trial it became evident that the definition agreed to by the parties was not sufficiently precise to answer the question critical to this litigation: does "skin permeable form of fentanyl base" as used in the '580 patent include solutions of fentanyl at pHs of 7.0 or lower? As one of Mylan's scientific experts, Dr. Jonathan Hadgraft, stressed: "I find just describing something as skin permeable is an ambiguous statement." (Hadgraft 9/4/03, II at 112.) "You have to read [permeable] in the context in which it's written." Id. at 109.

Claim construction is an issue of law. Markman v. Westview

Instruments, Inc., 517 U.S. 370, 391 (1996). In determining the meaning of disputed claim language, a court looks first to "the intrinsic evidence of record," examining, in order, the claim language itself, the specification, and the prosecution history. Interactive Gift Express, Inc. v. Compuserve Inc., 256 F.3d 1323, 1331 (Fed. Cir. 2001) (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)). On the rare occasion that intrinsic evidence does not settle the meaning of a claim limitation, then extrinsic evidence may be considered. Id. at 1332.

The words used in claim language are presumed to have "the ordinary and customary meanings attributed to them by those of ordinary skill in the art," unless an express intent appears otherwise. Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc., 334 F.3d 1294, 1298 (Fed. Cir. 2003). This presumption is a heavy one, Amgen Inc. v Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1327 (Fed. Cir. 2003), but may be overcome where the patentee has specifically set forth a definition of the term different from its ordinary and customary meaning, or where the patentee has clearly disavowed the apparent scope of coverage. Brookhill-Wilk, 334 F.3d at 1299.



A construing court must be careful not to read into the claims limitations that appear in the specification. See Interactive Gift, 256 F.3d at 1331-32 (recognizing a fine line between reading claim in light of specification and reading limitation into claim from specification, quoting Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1186 (Fed. Cir. 1998)); see also Amgen, 314 F.3d at 1325; Laitram Corp. v. NEC Corp., 163 F.3d 1342, 1348 (Fed. Cir. 1998) (interpreting what is meant by word in claim must not be confused with adding extraneous limitation appearing in specification, which is improper, quoting Intervet Am., Inc. v. Kee-Vet Labs., Inc., 887 F.2d 1050, 1053 (Fed. Cir. 1989)). “Advantages described in the body of the specification, if not included in the claims, are not per se limitations to the claimed invention.” Brookhill-Wilk, 334 F.3d at 1301 (quoting Vehicular Techs. Corp. v. Titan Wheel Int’l, Inc., 141 F.3d 1084, 1096 (Fed. Cir. 1998) (Newman, J., dissenting)).

Claims are construed the same for both invalidity and infringement. Amgen, 314 F.3d at 1330. Terms that appear in multiple claims should be construed consistently for each claim. Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1342 (Fed. Cir. 2001).

"Skin permeable form" appears in each of the asserted claims. The term is used in all of the claims of the '580 patent. As was demonstrated at trial, from the point of view of one skilled in the art, the phrase "skin permeable form" is ambiguous, and must be interpreted in context. The base form of fentanyl has been generally described as the skin permeable form of the drug. See Samir D. Roy & Gordon L. Flynn, Transdermal Delivery of Narcotic Analgesics, 7 Pharmaceutical Research 842, 847 (1990) (PX 28). The asserted claims however specify the use of a skin permeable form of fentanyl base. If "skin permeable form" means merely "the base form of the drug," the term is redundant.

Where terms chosen by the patentee are sufficiently unclear that one cannot determine the scope of the claim from the language used, statements in the specification or prosecution history may be used to define the scope of the claim. See Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 990 (Fed. Cir. 1999). The Court therefore looks to the specification to see if the meaning of skin permeable form is found there.

In column 3 the inventors state:

[w]e have discovered that fentanyl citrate, the form in which fentanyl is presently administered, has such a low skin permeability that it is not at all suitable for transdermal delivery even with the use of permeation enhancers. Instead we have found that, in order to obtain the delivery rates noted above, the drug should be incorporated in the transdermal therapeutic system in the form of the base.

'580 patent at 3:10-17. For purposes of the '580 patent, fentanyl citrate is considered by the inventors not to be a skin permeable form of the drug. The specification is usually dispositive as to the meaning of a disputed term. Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1325 (Fed. Cir. 2002) (quoting Vitronics, 90 F.3d at 1582).

Even if the term were clear on its face, the intrinsic evidence must be examined to determine whether "a deviation from the clear language of the claims is specified," if for example, a patentee has relinquished a particular claim construction in an argument to overcome or distinguish a reference. Interactive Gift, 256 F.3d at 1331. The Gale Declaration, submitted during the second reexamination, specifically disclaims fentanyl citrate: "we specifically stated in the '580 patent [fentanyl citrate] was unsuitable for transdermal delivery." (Gale Decl. (PX 10) ¶ 11; see also id. ¶ 10 ("The '580 patent . . . discloses that the only form of fentanyl that was then being

used for medical purposes, fentanyl citrate, is unsuitable for transdermal administration because of its low transdermal flux").) In disclaiming fentanyl citrate as a skin permeable form, Gale referred to the fentanyl solution contemplated by the Keith matrix as having a pH of 6.5 to 7.0, and noted that the fentanyl in this solution "would exist virtually completely in the form of fentanyl citrate." Id. ¶¶ 7-9.

"[W]here the patentee has unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of the surrender." Omega Eng'g, Inc. v. Raytek Corp., 334 F.3d 1314, 1324 (Fed. Cir. 2003). Read in light of the specification, and the file wrapper's specific disclaimer, the "skin permeable form" that is claimed excludes fentanyl citrate.

Mylan points out, accurately, that the fentanyl that actually passes through the skin is in the form of the base, no matter what the pH of the fentanyl solution is. From this point it argues that the claim language cannot be construed to exclude solutions of fentanyl citrate, because citrate is not what is transdermally administered. But referring to the permeability of fentanyl means referring to its permeability in solution,

because undissolved fentanyl will not pass through the skin. See, e.g., Hadgraft 9/5/03, I at 101. A skin permeable form cannot be undissolved fentanyl base, but must be fentanyl base in solution, even if what actually passes through the skin are molecules of fentanyl base. According to the intrinsic evidence, in the '580 patent's claims that solution is limited by the exclusion of solutions of pH 7.0 or lower.

Alza has urged the Court to construe "skin permeable form" as including the concept of minimizing residual drug. Although the patent specification clearly iterates drug minimization as a goal of the invention ('580 patent at 1:58-60; 2:23-26), the claims contain no limitation requiring minimization of drug loading. Indeed, claim 61.31 contains a limitation specifying that the drug reservoir contain between 0.1 and 50% by weight of a skin permeable form of fentanyl base, hardly an indication of minimal drug loading. There is no suggestion in the specification that "skin permeable form" means a form of fentanyl base in which adequate flux is achieved with the minimum amount of drug. Nor does the prosecution history supply such a definition. To read the asserted claims of the '580 patent as including a drug minimization limitation would be a classic example of "'adding an extraneous limitation appearing

in the specification, which is improper.'" Laitram, 163 F.3d at 1348 (quoting Intervet Am., 887 F.2d at 1053).

The Court construes "skin permeable form" as fentanyl that is in a form that can pass through the skin, excluding solutions of fentanyl citrate.<sup>4</sup>

## **B. Infringement**

Mylan's fentanyl patch is a monolith transdermal system that contains base fentanyl. It is designed to be bioequivalent to Duragesic®, and in order to be approved by the FDA must

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<sup>4</sup> Because the claim language can be construed from an examination of the intrinsic evidence, consideration of extrinsic evidence is unnecessary. See Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583 (Fed. Cir. 1996) (improper to rely on extrinsic evidence where analysis of intrinsic evidence resolves ambiguity in disputed claim term); see also CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1368 (Fed. Cir. 2002) (unnecessary to examine expert testimony if ordinary meaning of term can be resolved by resort to intrinsic evidence and dictionary definitions). The Court notes that Mylan's expert Dr. Hadgraft interpreted the '580 patent's use of "skin permeable form" in the patent's claims as referring to the skin permeability coefficient, that value derived from flux and concentration. (Hadgraft 9/4/03, II at 114.) Dr. Hadgraft further interpreted the patent as excluding fentanyl citrate from the definition of skin permeable. Id. at 121. Dr. Hadgraft's interpretation of the phrase as used in the patent is consistent with the Court's claim construction. See Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309 (Fed. Cir. 1999) (entirely appropriate for court to consult trustworthy extrinsic evidence to ensure claim construction is not inconsistent with understanding in pertinent technical field); accord Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1346 (Fed. Cir. 2003).

deliver fentanyl in the same way that Duragesic® does.

Duragesic® practices the '580 patent.

Specifically, Mylan's patch delivers an analgetically effective rate at a steady state for a period of three days, and has sizes that correspond to the sizes of Duragesic® patches. The Mylan patch is designed for delivery through intact skin. It has a drug reservoir/contact adhesive layer which serves to adhere the patch to the skin as well as to contain the drug.

The Court denied summary judgment on infringement in part because it could not hold as a matter of law that the drug reservoir/contact adhesive layer in the monolith embodiment of the '580 patent functioned as the means for maintaining the drug reservoir on the skin, based on the declaration of Dr. Hadgraft. Alza Corp. v. Mylan Labs., Inc., No. 02-cv-20, slip op. at 3-5 (D. Vt. Aug. 18, 2003). At trial however, Dr. Hadgraft acknowledged that a person skilled in the art would understand that a drug reservoir/contact adhesive layer could serve to maintain the patch on the skin, although he contended that given the state of adhesive technology at the time the '580 patent was issued, a person skilled in the art would not "necessarily" have linked such a layer to the means for maintaining. (Hadgraft 9/4/03, II at 37.)

Alza has demonstrated that a function of the drug reservoir/contact adhesive layer in its simple monolith is to adhere the reservoir to the skin. That it may or may not function poorly is not at issue, nor is the fact that some monolith or multilaminate patches have employed additional means for adhering the patch to the skin. The issue is whether it would have been clear to one skilled in the art that the drug reservoir/contact adhesive layer of the monolith described in the '580 patent contained the structure that corresponded to the means for maintaining the reservoir to the skin. In the description of the monolith, no other structure could perform the function, which is of course, suggested by the words "contact adhesive" themselves.

Mylan has admitted that it intends to engage in the commercial manufacture and sale of its transdermal fentanyl patch before the expiration of the '580 patent. Alza is entitled to judgment that Mylan's ANDA for a transdermal fentanyl patch is an act of infringement. 35 U.S.C.A. § 271(e)(2).

## **II. Validity of the '580 Patent**

Mylan has argued that the '580 patent is invalid as having been anticipated by the Keith patent, as obvious based on the



prior art, and as having been procured by inequitable conduct.

"An issued patent enjoys a presumption of validity, 35 U.S.C. § 282, that can be overcome only through clear and convincing evidence." Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920 (Fed Cir. Feb. 13, 2004) (citing U.S. Surgical Corp. v. Ethicon, Inc., 103 F.3d 1554, 1563 (Fed. Cir. 1997)).

Invalidation based on anticipation or obviousness involves a two-step analysis, in which a court first construes the claims that are alleged to be anticipated or obvious, and then compares the construed claims to the prior art. Key Pharms. v. Hercon Labs. Corp., 161 F.3d 709, 714 (Fed. Cir. 1998). Claim construction is the same whether the issue is infringement or invalidity. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1330 (Fed. Cir. 2003).

#### **A. Anticipation**

Anticipation requires that "a single prior art reference discloses each and every limitation of the claimed invention." Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003).

##### **1. Skin permeable form of fentanyl base**

All of the asserted claims of the '580 patent require a "skin permeable form" of fentanyl base, construed by this Court

as fentanyl that is in a form that can pass through the skin, excluding solutions of fentanyl citrate. The Keith patent teaches one to prepare a solution containing fentanyl that is adjusted to a pH of 7.0 or below. Such a solution is at least 95% fentanyl citrate.

The '580 patent, as discussed above, excludes fentanyl citrate, with particular reference to the drug SUBLIMAZE®. SUBLIMAZE® has a pH of 7.5 or below. Thus one of ordinary skill in the art would understand that a solution of fentanyl with a pH of 7.5 or below is known as fentanyl citrate even though the solution includes a small fraction of fentanyl base. Moreover, the Gale Declaration, disclaiming fentanyl citrate solutions, specifies that solutions made according to Keith, with a pH of 7.0 or below, are not considered skin permeable forms of fentanyl, as that phrase is used in the '580 patent. (Gale Decl. ¶ 10, 11 (PX 10); see also Hadgraft 9/4/03, II at 125-26 (Gale Declaration indicates inventors of '580 patent did not consider solutions with pHs of 7 or lower to be skin permeable forms of fentanyl).)

Because the Keith patent does not disclose a "skin permeable form" of fentanyl within the meaning of the '580

patent, it lacks that limitation present in each of the asserted claims, and does not anticipate the '580 patent.

**2. Administration rate within the range of about 25 to 150 µg/hr**

Claim 59.15 requires a steady state administration rate within the range of about 25 to 150 µg/hr. The Keith patent teaches one to use "a therapeutically effective amount," Keith patent at 2:24-25, or "an appropriate amount," id. at 11:57, of fentanyl, described as an analgesic, id. at 3:54, and describes "sustained release of the drug at a relatively steady rate." Id. at 3:45. Thus, the Keith patent does not expressly provide specific rates at which fentanyl should be delivered to be analgetically effective. By instructing the artisan of ordinary skill to include a therapeutically effective amount of fentanyl in the matrix, however, the Keith patent implicitly instructs that person to consult the available literature or other references to determine a therapeutically effective amount and rate of fentanyl.

A prior art reference may anticipate without disclosing a limitation of the claimed invention "if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." Schering, 339 F.3d at 1377;

accord In re Cruciferous Sprout Litig., 301 F.3d 1343, 1349 (Fed. Cir. 2002). A limitation is inherent "if it is the 'natural result flowing from' the explicit disclosure of the prior art." Schering, 339 F.3d at 1379 (quoting Cont'l Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991)). As the Court in Continental Can explained:

[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. . . . Inherency, however, may not be established by probabilities or possibilities. . . . This modest flexibility in the rule that "anticipation" requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges.

Cont'l Can, 948 F.2d at 1268-69 (citations omitted).

Mylan offered the White, Hull and Kay papers on intravenous infusion of fentanyl to show what one of skill in the art would have been aware of when reading the reference to a "therapeutically effective amount" of fentanyl in the Keith patent. See C.J. Hull & A. Sibbald, Control of Postoperative

Pain by Interactive Demand Analgesia, 53 Brit. J. Anaesth. 385 (1981) (DX 1193); B. Kay, Postoperative Pain Relief, 36 Anaesthesia 949 (1981) (DX 1168); W.D. White, et al., Postoperative Analgesia: a Comparison of Intravenous On-Demand Fentanyl with Epidural Bupivacaine, 2 Brit. Med. J. 166 (1979) (DX 1176). Dr. Flynn set out to determine a therapeutically effective amount of fentanyl from these among other references available in 1983-84. The literature contained no information about transdermal administration of fentanyl. At the time there were no generally approved or acknowledged dosages for the transdermal administration of fentanyl. Cf. Key Pharms., 161 F.3d at 718 (sensible to look to FDA-approved dosages to determine amounts considered pharmaceutically effective).

Dr. Flynn reviewed the available literature, derived a range of dosages, and selected one "as a first estimate." He admitted that others of skill in the art could select other dosages. In fact when the Mylan scientists stepped up production of the Keith matrix they included a quantity of drug which did not follow Dr. Flynn's calculations and for which no scientific justification was provided. (Flynn 9/3/03, I at 88-90; Ackerman 9/3/03, II at 10-14.)

The dosage determination required analysis and research. Dr. Flynn hypothesized that the amount he selected to add to the matrix would deliver a therapeutically effective amount of fentanyl. In fact his subsequent flux study showed that his initial diffusion matrix made according to Keith did not deliver an analgetically effective dose of fentanyl. Further experimentation enabled him, and the Mylan scientists, to select a drug loading amount and a patch size that would deliver their targeted dosage across the skin.

At issue before the Court then, is whether such a trial and error process, commonly practiced by artisans of ordinary skill in their research and experimentation, is contemplated by the term "inherency," such that the prior art reference anticipates the claimed invention. The Court resolves "factual questions about the subject matter in the prior art by examining the reference through the eyes of a person of ordinary skill in the art, among other sources of evidence about the meaning of the prior art." Schering, 339 F.3d at 1377-78. The Court is satisfied that it was the common knowledge of those skilled in the art that pharmaceutical dosages could be derived from available references. A range of therapeutically effective dosages for the intravenous administration of fentanyl for

analgesia was also common knowledge. The Court has heard no evidence, however, that a therapeutically effective amount of fentanyl for transdermal administration was within the common knowledge of those skilled in the art in the 1983 or 1984.

As the testimony at trial made abundantly clear, deriving a therapeutically effective dose of fentanyl for transdermal administration involved substantial research and experimentation, and a considerable degree of analysis and insight. The Alza scientists, in developing Duragesic®, had to extrapolate from the available references in order to determine appropriate dosages for transdermal administration, as did Dr. Flynn and the Mylan scientists when they made a Keith diffusion matrix. The analgetically effective rate for transdermal administration of fentanyl was not known in the art.

To be sure, "[i]nherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art."

MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999). But failing to recognize an inherent characteristic or quality or functioning of an invention is quite distinct from having to sift through and analyze the available literature and then to experiment to arrive at a characteristic of an invention. Cf. In re Cruciferous Sprout, 301 F.3d at 1350, 1352

(sprout's cancer-fighting potential is inherent characteristic of the sprout; patent involving production and consumption of cruciferous seed sprouts invalid as anticipated).

Because the Keith patent does not disclose a steady state administration rate within the range of about 25 to 150 µg/hr, nor is the limitation inherent in the reference, the Keith patent does not anticipate claim 59.15 of the '580 patent.

### **3. Period of time in the range of about 3 days**

The Keith describes transdermal administration "over an extended period, typically 24 hours, and "over a prolonged period, typically 24 hours." Keith patent at 2:52-52; 3:44-48. Keith does not discuss administration of any drug for longer than 24 hours. Dr. Flynn considered that a person of ordinary skill in the art in 1983 would have contemplated administering fentanyl for a three day period because a three-day scopolamine patch was then on the market, and three-day estradiol and seven-day clonidine patches were being tested. (Flynn 9/2/03, II at 110.) Prior to the work that led to the development of Duragesic®, the longest reported instance of continuous delivery of fentanyl for analgetic purposes was seventeen hours, as reported in the White paper, Postoperative Analgesia. See W.D. White, et al., at 167. It was not common knowledge, or



inherent in the Keith patent, that fentanyl could be effectively delivered over a period of three days. Because the Keith patent does not disclose administration over an extended period of time in the range of at least about three days, nor is the limitation inherent in the reference, the Keith patent does not anticipate claims 59.11, 59.15 and 61.31 of the '580 patent.

#### **4. Enablement**

To be anticipatory, the prior art must enable one skilled in the art to make the invention "without an undue amount of experimentation." Helifix Ltd. v. Blok-Lok, Ltd., 208 F.3d 1339, 1348 (Fed. Cir. 2000). A prior art patent is presumed enabled. Amgen, 314 F.3d at 1355. The Court is convinced, however, that Alza has presented sufficient evidence of nonenablement to overcome the presumption.

Keith's patent in effect invited one of skill in the art to experiment with fentanyl in a diffusion matrix; Keith did not invent a fentanyl diffusion matrix. One of skill in the art could not, without undue experimentation, make a therapeutically effective transdermal fentanyl patch from the Keith teaching. Keith teaches one to make a transdermal fentanyl delivery system by using a ten-fold excess of an ionized form of the drug. Although that apparently was a workable system for

nitroglycerin, it did not take into account the different properties of fentanyl. When a ten-fold excess of a chosen amount of fentanyl citrate was incorporated into the diffusion matrix, it did not come close to delivering the chosen dose. The Mylan scientists did achieve the delivery of fentanyl base across the skin at analgetically effective rates from a matrix created according to the Keith formula, but only by departing from the teaching of Keith and adding an eighty-fold excess rather than a ten-fold excess of fentanyl to the matrix. This degree of tinkering with Keith demonstrates that the Keith patent is not enabled with respect to the transdermal delivery of fentanyl. See, e.g., Rowe v. Dror, 112 F.3d 473, 480 (Fed. Cir. 1997) (no anticipation where artisan of ordinary skill must guess about how one structure would substitute for another and whether substituted structure would be capable of performing according to claims of challenged patent).

Mylan has therefore failed to demonstrate by clear and convincing evidence that the '580 patent is invalid as anticipated by the Keith patent, because the Keith patent does not disclose a skin permeable form of fentanyl base as that phrase is used in the '580 patent; because the Keith patent does not disclose an analgetic dosage; and because the Keith patent

does not enable the creation of an analgetically effective fentanyl transdermal patch.

#### **B. Obviousness**

Mylan contends that because the Keith patent anticipates all of the elements of the asserted claims of the '580 patent, the asserted claims are also rendered obvious. That the Keith patent does not anticipate the asserted claims of the '580 patent has been addressed in the previous section. In the alternative, Mylan maintains that those elements of the asserted claims that were not anticipated would have been obvious to those of ordinary skill in the art.

An invention is obvious when "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.'" Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124 (Fed. Cir. 2000) (quoting In re Dow Chem., 837 F.2d 469, 473 (Fed. Cir. 1988)). An invention "is not obvious solely because it is composed of elements that are all individually found in the prior art," however. Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000). Obviousness is a legal determination, based on findings concerning the so-

called Graham factors: "(1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art;<sup>5</sup> and (4) secondary considerations, if any, of nonobviousness." McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362, 1368 (Fed. Cir. 2003) (citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)); accord Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., 357 F.3d 1319, 1334 (Fed. Cir. 2004).

#### **1. Scope and content of prior art**

"[T]he relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references." Ruiz v. A.B. Chance Co., 234 F.3d 654, 664 (Fed. Cir. 2000). A reason, suggestion or motivation to combine may be explicit or implicit, and may be found in the prior art references themselves, in the knowledge of those of ordinary skill in the art, or from the nature of the problem to be

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<sup>5</sup> The parties agree that the level of skill involved in the transdermal delivery of drugs is quite high: a Ph.D. in pharmacology, physiology, or pharmaceutical science or related fields, plus experience practicing in the field of transdermal drug delivery.

solved. Id. at 665. A showing of combinability must be clear and particular, id. (quoting In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999)), and the "factual inquiry whether to combine references must be thorough and searching." McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351-1352 (Fed. Cir. 2001). To prevent the use of hindsight based on the invention itself to invalidate the patent, this Court must be able to discern "reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). "There is no suggestion to combine, however, if a reference teaches away from its combination with another source." Tec Air, Inc. v. Denso Mfg. Mich. Inc., 192 F.3d 1353, 1360 (Fed. Cir. 1999).

Mylan has not shown a reason, suggestion or motivation to combine the teachings of Keith, to use solutions of fentanyl citrate and a ten-fold excess of drug, with any reference that teaches one to use the base form of the drug in solution. Michaels et al. did provide flux data for the base form of fentanyl, which has proven to be an adequate flux rate and in fact is within the flux rate claimed by the asserted device

claims of the '580 patent. Neither Keith nor Michaels offers a reason to combine the references, however. Michaels taught that drugs of high water and oil solubility can be expected to be quite skin permeable. Fentanyl is not such a drug. Michaels thus teaches away from using fentanyl transdermally, even though its relatively low skin flux has proven adequate for transdermal devices, given the drug's potency. Keith taught that a diffusion matrix should be made from neutral or slightly acidic solutions. Keith thus teaches away from using solutions of fentanyl base.

The artisan of ordinary skill might have been motivated to combine the Michaels reference giving skin flux data for fentanyl base with the White, Hull or Kay references giving intravenous dosage information for the ionized form of fentanyl in order to formulate a transdermal dosage amount for fentanyl base. That artisan would have recognized from a combination of the Michaels, White, Hull and Kay references that fentanyl base could theoretically be delivered at analgetically effective rates.

Mylan has failed to produce clear and particular evidence of the combinability of any or all of these references with Keith, however, given Keith's requirement of a neutral or

slightly acidic drug solution for its diffusion matrix.

Furthermore, those of skill in the art would have known that the conventional way of producing a transdermal patch at the time-- to use substantial excesses of drug, as exemplified by Keith-- posed a problem in attempting to craft a transdermal patch for the delivery of a potent narcotic such as fentanyl. For example, Dr. Flynn acknowledged that it was a matter of common sense to keep residual drug to the minimum physically possible when creating transdermal delivery systems for drugs that are both expensive and prone to abuse. (Flynn 9/3/03, I at 33.) The Keith teaching to use a ten-fold excess of drug would have discouraged those of ordinary skill in the art from employing this recipe for a transdermal patch that contained a potent narcotic.

## **2. Differences between claims and prior art**

The prior art taught the use of fentanyl citrate. The claims exclude the use of fentanyl citrate.

## **3. Secondary considerations**

The finding that Keith teaches away from the prior art references cited will defeat a claim of obviousness. Winner

Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000). Nevertheless, Alza has also shown objective evidence of nonobviousness: the long-felt but unsolved need for a continuous system of pain relief and the success of Duragesic®. See Ruiz, 234 F.3d at 663 (secondary considerations of nonobviousness include commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results) (citing Graham, 383 U.S. at 17-18).

Duragesic® answered a tremendous need for a continuous pain relief system for cancer patients, among others. Flynn 9/2/03, II at 136-37. It provided relief for patients who suffered from nausea and vomiting or were otherwise unable to swallow pills. It provided an alternative to intravenous administration. It provided the option of continuous administration for up to 72 hours.

Duragesic® has enjoyed a huge commercial success. Its sales have increased over the years that it has been on the market. Within three years of its launch, Duragesic® had nearly \$100 million in net trade sales. (PX 531.) Five years later, in 1999, Duragesic® had \$325 million in net trade sales. Id. For 2003, Janssen projected that net trade sales would exceed one billion dollars. (Eckhardt 8/25/03, II at 106-07; PX 531.)



When a patentee asserts that commercial success proves that its invention is nonobvious, the patentee must show a nexus between the commercial success and the patented invention. Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1392 (Fed. Cir. 1988). The '580 patent claims processes and devices for inducing and maintaining analgesia by the transdermal administration of fentanyl base at analgetically effective rates for extended periods of time. It is undisputed that Duragesic® practices the '580 patent. "When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." J.T. Eaton & Co. v. Atl. Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997) (citing Demaco, 851 F.2d at 1392-93). The burden thus shifted to Mylan to prove that Duragesic®'s commercial success was due to "factors extraneous to the patented invention, such as advertising or superior workmanship." Id. Although Mylan challenged the existence of a nexus, it failed to show that Duragesic®'s commercial success was due to factors extraneous to the claims of the '580 patent.

Given that this Court cannot find a suggestion or motivation to combine the teachings of the Keith patent with other prior art references, that the Keith patent in any event teaches away from the use of fentanyl base in solution for transdermal delivery, and that secondary considerations supply objective evidence of nonobviousness, the Court concludes that Mylan has failed to provide clear and convincing evidence of obviousness.

### **C. Inequitable Conduct**

Mylan has also charged that the '580 patent is unenforceable because Robert Gale, co-inventor of the '580 patent, engaged in inequitable conduct before the United States Patent Office. To prove inequitable conduct, Mylan must have provided clear and convincing evidence of "'affirmative misrepresentations of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive.'" Purdue Pharma L.P. v. Boehringer Ingelheim GMBH, 237 F.3d 1359, 1366 (Fed. Cir. 2001) (quoting Baxter Int'l, Inc. v. McGaw, Inc., 149 F.3d 1321, 1327 (Fed. Cir. 1998)). Before a court can judge whether the conduct is so culpable as to render the patent unenforceable it must make threshold factual determinations both of

materiality and of intent. Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1324 (Fed. Cir. 2000); accord Purdue Pharma, 237 F.3d at 1366.

During the second reexamination of the '580 patent, Gale submitted a declaration, pursuant to 37 C.F.R. § 1.132, in which he distinguished the Keith patent from the '580 patent. Mylan contends that the declaration contained affirmative misrepresentations and false information. There is no dispute that the Gale Declaration in general was "material" to the 1998 reexamination of the '580 patent. E.g., Rohm & Haas Co. v. Crystal Chem. Co., 722 F.2d 1556, 1571 (Fed. Cir. 1983) (no room to argue that submission of false affidavits to PTO is not material). Specifically, Mylan claims that the following statements in Gale's Declaration were false or misleading:

- . . . fentanyl present in the Keith et al. matrix would exist virtually completely in the form of fentanyl citrate. (Gale Decl. ¶ 9 (PX 10).)<sup>6</sup>

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<sup>6</sup> The full text of paragraph 9 states:  
Because fentanyl has a pK of 8.3 the fentanyl present in the Keith et al. matrix would exist virtually completely in the form of fentanyl citrate. As a result, to the extent that the Keith patent could be considered to disclose making a transdermal fentanyl delivery system by including fentanyl in the diffusion matrices of the Keith patent, such a system would be unsuitable for administering fentanyl at

- . . . such a [Keith] system would be unsuitable for administering fentanyl at analgetically effective rates. Id.
- The '580 patent, at col. 3, lines 6-14 and col. 1, lines 22-25, discloses that the only form of fentanyl that was then being used for medical purposes, fentanyl citrate, is unsuitable for transdermal administration because of its low transdermal flux. Id. ¶ 10.<sup>7</sup>
- . . . the Keith patent suggests the production of a diffusion matrix containing fentanyl citrate, which we specifically stated in the '580 patent was unsuitable for transdermal delivery, even with permeation enhancers. Id. ¶ 11.<sup>8</sup>

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analgetically effective rates.

<sup>7</sup> The full text of paragraph 10 states:  
In particular, Keith et al. fail to recognize that, as disclosed in the '580 patent, fentanyl can exist in different chemical forms that exhibit different permeabilities through skin. The '580 patent, at col. 3, lines 6-14 and col. 1, lines 22-25, discloses that the only form of fentanyl that was then being used for medical purposes, fentanyl citrate, is unsuitable for transdermal administration because of its low transdermal flux. The specification then proceeds to describe aqueous and non-aqueous diffusion matrices in which fentanyl can be stored and delivered in a skin permeable form. Keith et al., however, fail completely to recognize the importance of these features and, in fact, disclose diffusion matrices that administer the unsuitable fentanyl citrate.

<sup>8</sup> The full text of paragraph 11 states:  
Thus, in contrast to our disclosure and claims in the '580 patent, the Keith patent suggests the production of a diffusion matrix containing fentanyl citrate, which we specifically stated in the '580 patent was unsuitable for transdermal

- . . . the Keith patent would not suggest to or enable one of ordinary skill in this art to make and use a device or process that would transdermally administer a "skin permeable form" of fentanyl (or derivatives thereof) to a human at an analgetically effective rate for a period of time sufficient to induce and maintain analgesia. Id.
- Data generated in [Alza's skin permeability] studies supported the conclusion that the skin permeability of fentanyl citrate was too low to permit analgetically effective transdermal fentanyl administration rates to be obtained from reasonably sized transdermal systems. Id. ¶ 12.<sup>9</sup>

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delivery, even with permeation enhancers. It is clear to me from reading the Keith patent that Keith et al. had no appreciation of either a) the difference between the use of fentanyl citrate and forms of fentanyl suitable for transdermal administration, or b) the use of a fentanyl-containing matrix that can store and transdermally administer fentanyl in such a suitable form. I believe that the disclosure of the Keith patent would not suggest to or enable one of ordinary skill in this art to make and use a device or process that would transdermally administer a "skin permeable form" of fentanyl (or derivatives thereof) to a human at an analgetically effective rate for a period of time sufficient to induce and maintain analgesia. Thus, I believe that the Keith patent fails to disclose or suggest the invention claimed by the '580 patent.

<sup>9</sup> The full text of paragraph 12 states:  
 Skin permeability studies conducted by ALZA researchers provided the basis for the comments in the '580 patent (col. 3, lines 10-14) regarding the low skin permeability of fentanyl citrate and its unsuitability for transdermal administration. Data generated in these studies supported the conclusion that the skin permeability of fentanyl citrate was too low to permit analgetically

- I have reviewed Dr. Lee's memo and concur in Dr. Lee's conclusion on p. 5 that, "In general, much higher flux is observed with base Fentanyl than its citrate salt. It would be recommended to pursue studying with base drug." Id. ¶ 13.<sup>10</sup>  
Of these seven statements, the first and fourth are in fact accurate, according to the trial testimony and exhibits. The experts for both parties agreed that the fentanyl present in a Keith matrix at pH 6.5 to 7 would be almost entirely in the form of fentanyl citrate, and the '580 patent stated that fentanyl citrate was unsuitable for transdermal delivery, even with permeation enhancers. ('580 patent at col. 3: 10-14.)

Based on his interpretation of the Keith patent, that it directed one to make a diffusion matrix containing fentanyl citrate, and his belief as stated in his patent that fentanyl

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effective transdermal fentanyl administration rates to be obtained from reasonably sized transdermal systems. Copies of laboratory notebook entries documenting these studies are attached as Exhibit 2.

<sup>10</sup> The full text of paragraph 13 states:  
These data were summarized in a 1983 memo prepared by one of the coinventors of the '580 patent, Dr. Eun Soo Lee, a copy of which is attached as Exhibit 3. I have reviewed Dr. Lee's memo and concur in Dr. Lee's conclusion on p. 5 that, "In general, much higher flux is observed with base Fentanyl than its citrate salt. It would be recommended to pursue studying with base drug."

citrate was unsuitable for transdermal delivery, Gale opined in the second statement that the Keith system would be unsuitable for administering fentanyl at analgetically effective rates. In the fifth statement Gale again opined, using the language "skin permeable form" employed by the '580 patent to exclude fentanyl citrate, that the Keith patent would not suggest or enable the skilled artisan to make an effective fentanyl transdermal patch. The Court is convinced that Gale sincerely held these beliefs then and holds these beliefs now, in accordance with the teachings of his patent.

Mylan objects to the seventh statement as creating a misleading impression that fentanyl base was the only acceptable form for all potential transdermal systems, when in context Dr. Lee was recommending the use of fentanyl base in an ethanol and water system (Lee Mem. at 5 (PX 10, Attach. 3)). The Court disagrees: whether cropped or in context, Dr. Lee's conclusion--and Gale's concurrence with it--cannot reasonably be construed as suggesting that fentanyl base was the only route to transdermal success, whether in aqueous or non-aqueous systems. The part of Dr. Lee's conclusion that Gale quoted in his Declaration uses the phrases "in general" and "recommended to

pursue studying." The seventh challenged statement is also an accurate statement of fact and belief.

As to the third statement, describing the '580 patent's disclosure, the patent in fact discloses at column 3, lines 10 to 14, that fentanyl citrate has such a low skin permeability that it is not at all suitable for transdermal delivery ('580 patent at col. 3: 10-14 (emphasis supplied)). Thus Gale's Declaration inaccurately equated transdermal flux with skin permeability in restating the language of the patent. The Court is unable to find that this inaccuracy was material. Later in the Declaration Gale refers to skin permeability in the same context. (Gale Decl. ¶ 12.) There were numerous references at trial to the imprecision of the phrase "skin permeable," but the Court does not find that Gale deliberately used the phrase "low transdermal flux" in this context with an intent to mislead.

In sum, six of the seven statements proffered by Mylan as false and misleading are accurate statements of fact or belief, and one is an immaterial discrepancy. The sixth statement, however, although literally accurate, had the potential to mislead the patent examiner. Gale stated that data generated in Alza's skin permeability studies "supported the conclusion that the skin permeability of fentanyl citrate was too low to permit



analgetically effective transdermal fentanyl administration rates to be obtained from reasonably sized transdermal systems." Id. The statement is literally true. These data did support Dr. Lee's and others' conclusions in 1983 that they should proceed with the base form of fentanyl because they could not achieve their design goals of maximum flux with minimal drug loading using fentanyl citrate.

Gale admitted at trial, however, that as of 1998 when his declaration was submitted, he knew that the data also showed that fentanyl, at the pHs taught by the Keith patent, would in fact have high enough skin permeability "to permit analgetically effective transdermal fentanyl administration to be obtained from reasonably-sized transdermal systems." (Gale 8/27/03, I at 94.) In fact, as Mylan's expert Dr. Norman Weiner testified, the peak flux of fentanyl occurs in saturated solutions at pH 7.0. (Weiner 9/2/03, I at 35-40, 47.) A Keith fentanyl transdermal system might not have been pretty, it might not have been marketable, it might have contained massive amounts of residual drug, but it could have gotten an analgesic dose of fentanyl across an area of skin.

The statement, although literally true, had the potential to mislead the patent examiner. It was material; the patent

examiner based his decision to issue the reexamination certificate on the fact that "the citrate form of fentanyl has a very low level of transdermal permeability," although he referenced the '580 patent and an English translation of a Japanese patent for that statement, not Gale's Declaration. (PX 8, tab 8 at 2.)

At issue then, is whether the evidence demonstrated an intent to deceive. In general, "a lesser quantum of evidence of intent is necessary when the omission or misrepresentation is highly material." Amgen, 314 F.3d at 1358. Of course, "there must be some threshold showing of intent to be balanced." Id. Because direct evidence of deceitful intent is rare, intent is usually "proven by inferences drawn from facts, with the collection of inferences permitting a confident judgment that deceit has occurred." GFI, Inc. v. Franklin Corp., 265 F.3d 1268, 1274 (Fed. Cir. 2001).

The evidence of intent to deceive is extremely weak, if present at all. Alza's patent attorney, when informed of the Keith patent, requested reexamination of the '580 patent in light of the Keith reference. In context, the statements in Gale's declaration were true. No information was omitted. No information was affirmatively misstated. Gale's declaration

focused on the key distinction between his patent and the Keith patent, that Keith taught the use of a neutral or slightly acidic solution of fentanyl, which made it an unsuitable system for the administration of fentanyl in Gale's opinion, as he stated in the '580 patent. In light of all the circumstances, the Court cannot find that Gale acted with the requisite deceitful intent when he failed to point out that the data he submitted to the patent examiner included values that would suggest that one could also achieve an adequate flux in a transdermal system that used a sufficiently large amount of fentanyl citrate.

Because Mylan has failed to prove by clear and convincing evidence that the Gale Declaration contained material misrepresentations made with an intent to deceive, it has not shown that Alza engaged in inequitable conduct in the prosecution of the '580 patent.

### **III. Conclusion**

For the reasons stated, the Court concludes that Mylan's ANDA filing for a generic version of Duragesic® infringes claims 27.25, 59.11, 59.15 and 61.31 of the '580 patent. The '580 patent is not invalid as anticipated by the Keith reference. The '580 patent is not invalid as having been made obvious by

the Keith reference, either standing alone or in combination with other prior art. The '580 patent is not unenforceable as having been procured by inequitable conduct. Because infringement has occurred, the effective date of any approval of Mylan's ANDA product shall be no earlier than the date of the expiration of the '580 patent family. The Defendants are enjoined from making, using, offering to sell, selling within the United States or importing into the United States the fentanyl transdermal patches described in ANDA No. 76-258.

Dated at Burlington, Vermont this 25<sup>th</sup> day of March,  
2004.

/s/ William K. Sessions III

William K. Sessions III  
Chief Judge